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Original Research Article

Weight of Evidence of Long-Term Effects of Heavy Metals on the Cardiovascular System at a Population Level

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ABSTRACT

Heavy metals' chronic exposure is a major contributor to cardiovascular diseases (CVD) at the population level, and regions with high levels of heavy metals' contamination showed increased rate of mortality rate from cardiovascular diseases. Among different heavy metals; Arsenic, Lead, Mercury, and Cadmium are the most toxic to human health. The results of recent studies of the correlation between the four heavy metals and CVD are inconsistent with those of earlier studies and the general picture of the correlation between exposure to heavy metals and CVD presented by these studies is either inconsistent or not conclusive. Therefore, the purpose of the present paper is to weigh the amount of evidence presented in the literature for an association between each heavy metal and five cardio-vascular diseases: Coronary heart disease, cerebro-vascular disease, peripheral arterial disease, hypertension, and atherosclerosis.

Key words: Heavy Metals, Cardiovascular diseases, Toxicity, Weight of Evidence, Bradford Hill criteria

INTRODUCTION

The morality rate for cardiovascular diseases (CVD) has globally increased to the point that it is now recognized as a worldwide health problem. Of the many risk factors for CVD, the environment is one of the most important.[1] Risks from the environment have always been a major concern for human health, but until recently, the environmental risks posed by heavy metals were not well understood. However, the risks these metals posed began to draw scientists' attention after several serious accidents occurred, such as death from exposure to high doses of volatile metallic mercury, [2] and increased cases death among workers of industries containing lead products. [3]

The heavy metals best known for their many adverse effects are arsenic, lead, mercury and cadmium, which can cause neurotoxicity - a common adverse health outcome- nephrotoxicity, lung toxicity, hepatotoxicity, and other serious health problems. [2-5] While a common adverse health outcome from chronic exposure to heavy metals is cancer, CVD is another that is just as important. Several CVDs, including hypertension, atherosclerosis, coronary heart disease, and cerebro-vascular

disease have been reported to be caused by exposure to heavy metals. [6,7]

These four heavy metals are highly toxic, even at relatively minor levels of exposure. [8] Because of their high toxicity, they are among the top-ranked toxic materials listed in the U.S Agency for Toxic Substances and Disease Registry (ATSDR). [9] Yet, they continue to be widely used in various industries. Examples of heavy metals used in industrial products are: lead use in batteries; cable coverings; and glass making. [3] Cadmium is used in ceramics; and in glasses. [5] Arsenic is used in the production of wood preservatives; herbicides and insecticides. [4] Mercury is used to produce batteries; drugs and dental restorations; electric light bulbs; and thermometers and manometers. [2]

These metals are present almost everywhere. They have been used for thousands of years, [10] and have leaked into the environment from different manufactured products and from industrial waste, and are persistent in the environment. Their ability to bio-accumulate in the human body and other organisms facilitates their transfer through the food chain with the result that humans are always at a high risk of being in contact with them. [8] Thus, chronic exposure of the public to these metals is very likely to happen and long-term side effects are probable, including CVD. The continuous exposure of the general population to such heavy metals through the environment, including, but not limited to drinking water, contaminated air, soil and food has increased the incidence of CVD. [1,10]

Yet, the results of recent studies [11-13] examining the correlation between the four heavy metals and CVD are inconsistent with earlier studies. [14-16] This may be due to the use of more systematic epidemiological methods and more developed detection systems in recent studies, and the fact that many earlier studies were merely case reports or lacking control groups. The general picture of the correlation between exposure to heavy metals and CVD presented by many studies is either not consistent or not conclusive. Therefore, the purpose of this paper is to determine from the literature the weight of evidence for a correlation of each heavy metal to five cardio-vascular diseases: Coronary heart disease, cerebro-vascular disease, peripheral arterial disease, hypertension and atherosclerosis.

The strength of the association between a CVD and a heavy metal differs from one heavy metal to the other and from one CVD to the other. However, in the epidemiological or ecological studies that have been conducted, the results of an association are inconsistent. For example, some studies found a strong correlation of high mercury content in hair with coronary heart diseases and with CVD mortality. [17,18] On the other hand, other studies revealed no correlation between mercury concentrations in toenails and coronary heart disease, stroke, or total cardiovascular disease. [12]

MATERIALS AND METHODS

Procedure

The procedure used in this study is to review the ATSDR toxicological profile of the four heavy metals; to review articles about a single heavy metal effects, or review articles about the effects of heavy metals in general; and to review articles presenting original research that clearly support or refute a correlation between exposure to a heavy metal and CVD. The conclusions are based on the strength of evidence for a correlation of each heavy metal with a specific CVD.

Criteria for selecting literature

1. Publications with data based on human subjects (epidemiological studies taking into account only

population level and excluding occupational related data).

2. Four heavy metals: arsenic, lead, mercury, and cadmium; these four heavy metals are among the highest ranked in the toxicity list of the ATSDR.
3. Five categories of cardiovascular diseases: hypertension, atherosclerosis, coronary heart diseases, cerebro-vascular diseases, and peripheral arterial diseases.
4. Review articles that meet the criteria of items 1-3.
5. Articles from peer-reviewed journals, with an impact factor of 2.0 or more.
6. Related articles with specific characteristics (e.g., geographical region, large cohort sample size, and long-term follow-up).
7. The ATSDR toxic profiles for the four heavy metals.

Sir Austin Bradford Hill's criteria for causality or the association of a factor with a disease was considered, [19] and the first 2 characteristics; the strength of an association and degree of consistency were selected for the present study. The other seven characteristics are not compatible with this study as some of them are more likely to happen in clinical, experimental or observational studies as is pointed out in the Discussion. The evidence for an association between a heavy metal and a CVD varies between studies. For each relationship of a heavy metal and a CVD, studies show either a strong, a moderate or a weak association. We summarized the association in each relationship by making a qualitative evaluation of the strength of the relationship based. Our evaluation is based on: 1) the number of studies showing an association, 2) the strength of an association in studies with positive results, 3) the type of the study (case report, cohort, case-control), and 4) the ratio of studies establishing a positive relationship of a heavy metal to a CVD to studies failing to establish such a relationship. Weak, moderate, and strong associations are qualitative and quantitative criteria.

Criteria for determining the strength of evidence for an association

Weak Evidence

- The majority of studies are case report studies.
- There are few correlation studies with no support from case-control or cohort studies
- The number of published articles establishing an association is smaller than the number failing to establish an association
- In studies that do establish an association, the association is either weak or statistically insignificant.

Moderate Evidence

- There is some degree of inconsistency for an association; while some studies show an association with clear and positive evidence, another equivalent number of studies do not show such an association.
- There are few studies establishing a statistically significant association.

Strong Evidence

- The number of studies supporting an association is greater than the number that do not, and the evidence for an association is statistically significant.

We reviewed the selected articles to determine the strength of an association based on criteria above in order to weigh the amount of evidence for the five heavy metals associated with CVDs. These associations are found in the literature, but are not described systematically. Moreover, there is no article, to our knowledge, that

weigh the strength of such associations, the way it is presented in this study. In addition, the contra-positive results usually do not provide conclusive evidence for an association about the specific effects of these heavy metals on the CVD in question.

RESULTS

The relationship between the four heavy metals and the five CVDs in question are shown in Figure 1. Figure 2 shows the relationships between the five CVDs, with a representation of the effect of heavy metals on each of the CVDs. Figure 3 shows the molecular pathways by which a heavy metal might cause a certain CVD, and that some heavy metal might share the same pathway.

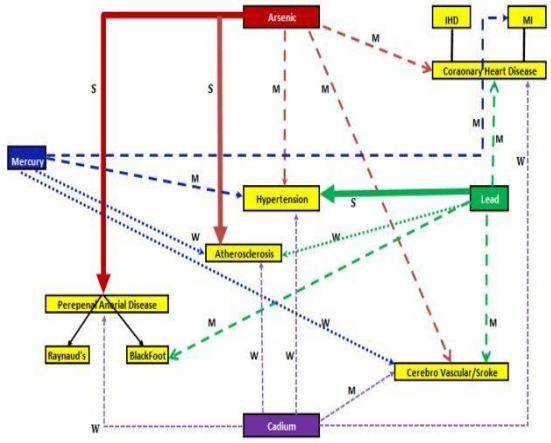

Figure 1: Illustration of the four heavy metals' associations with CVDs by their weight of evidence.

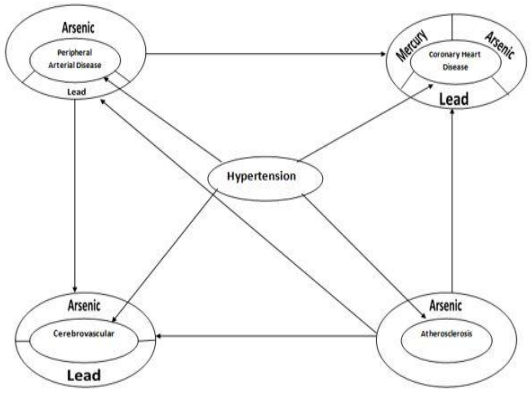

Figure 2: Each circle represents a disease, circled by heavy metals associated with it. The more ''space & size'' the heavy metal occupy in a circle, the more evidence of an association.

Table 1: Weight of evidence of heavy metals' associations with CVDs.

	Hypertension	Atherosclerosis	Coronary Heart Disease	Cerebro-Vascular	Peripheral Arterial Disease
Arsenic	Moderate [1, 4, 10, 13]	Strong [1, 4, 20, 21]	Moderate [1, 4, 13, 20-23]	Moderate [4, 13, 16, 20, 23]	Strong [4, 10, 16, 20, 23, 24]
Lead	Strong [1, 3, 25-27]	Weak [1, 3]	Moderate [1, 3, 27]	Moderate [1, 3, 6, 27]	Moderate [1, 3, 27]
Cadmium	Weak [1, 5, 14, 15, 28-30]	Weak [1, 5]	Weak [1, 5]	Moderate [1, 5, 6, 11]	Weak [1, 5, 16]
mercury	Moderate [1, 2, 7, 17, 25, 31]	Weak [1, 2, 7, 12, 17, 18, 31]	Moderate [2, 7, 10, 12, 17, 18, 25, 31]	Weak [2, 12, 31]	

According to the literature reviewed, hypertension is strongly associated with lead, moderately with arsenic and mercury, and weakly with cadmium. Atherosclerosis, on the other hand, is only strongly associated with arsenic but weakly with the other four heavy metals.

Table 2: CVDs acting as risk factors for other CVDs

Risk factor	Outcome			
Hypertension	Atherosclerosis [32, 33]	Coronary Heart Disease [34, 35]	Cerebrovascular [33, 36]	Peripheral Arterial Disease [37]
Atherosclerosis		Coronary Heart Disease [38, 39]	Cerebrovascular [40]	Peripheral Arterial Disease [41]
Peripheral Arterial Disease		Coronary Heart Disease [42, 43]	Cerebrovascular [42, 43]	

Peripheral arterial disease is strongly associated with arsenic, moderately with lead, weakly with cadmium, and not at all with mercury. It is interesting that for coronary heart diseases, three of the heavy metals are moderately associated, one exception being cadmium, which has weak association with the disease.

Stroke or cerebro-vascular disease is moderately associated with lead, arsenic, and cadmium but weakly associated with mercury. Figure 1 show these association, and Table 1 summarize the findings of the associations based on studies used in this articles.

Hypertension and atherosclerosis are risk factors for many CVDs, and these causative relations are shown in Table 2. It is important to note that peripheral arterial disease increases the risk of coronary and cerebro-vascular disease. Figure 2 was developed based on the information provided in Tables 1 and 2. In Figure 2, we present a prediction scenario in which one CVD can potentially progress to another in given conditions, especially when a heavy metal is associated with one or both of the related CVDs. Arsenic and lead, the heavy metals that for which there is the strongest evidence of a relationship, are linked to hypertension and atherosclerosis respectively.

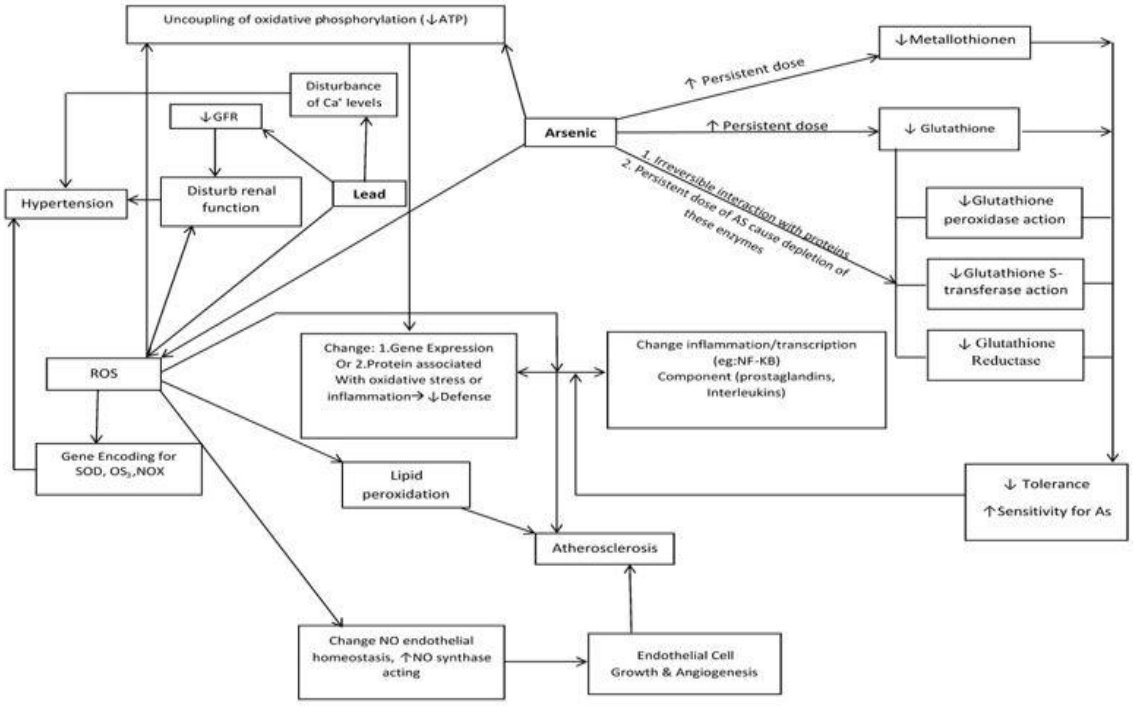

Figure 3: Crtitical pathways of toxicity leading to CVDs by two heavy metals

Figure 3 is an attempt to extrapolate to multiple exposures of two or more heavy metals occurring at the same time or even over two different periods of time, when the effect on a specific organ may be accumulative (i.e. additive or synergistic). The effect depends on the mode of action for each metal and is explained at greater length in discussion that follows below.

DISCUSSION

The current work drives conclusions from the information provided in the literature on the effect of heavy metals on CVDs. We suggested a degree of association between heavy metals and different CVDs based on the magnitude of evidence found in the literature for each of such associations. The criteria we followed in our methods was to help categorize each relationship after

reviewing studies and reviewing ATSDR profiles specific to the four heavy metals selected for this study.

Using Sir Austin Bradford Hill criteria for establishing causality, this study was only compatible with two out of nine criterions mentioned by Hill. [19] The first criterion is the strength of the association, which is defined as the proportional increase of disease or death in those who are exposed to those who are not exposed holding other factors constant. This criterion has been expressed in many studies using different measures such as relative risk, odds ratio, hazard ratio, and incidence rate. The second criterion is the consistency of the association, which reflects how much reliable an association can be if it's been repeatedly observed by different persons, in different places, circumstances and times. Other criterions are not compatible with this study. The third criterion is specificity, which is explained as if the association is limited to specific subjects, sites and types of disease. It is not applicable because associations of heavy metals found in literature were not specific to a particular population, diseases, or conditions. The fourth criterion is temporality. Temporality is difficult to establish in this study because we only considered studies done on population exposures, and not on industrial or occupational exposure studies, where temporality is possible to establish if workers' exposure is monitored along the duration of time of their work. Furthermore, this study meant to evaluate the chronic low-dose effect of heavy metals on CVDs, and it is very difficult to know when the exposure start or end. Therefore, most of studies done for such conditions are ecological, cross-sectional, and case-control.

The fifth and sixth characteristics are biological gradient and biological plausibility, respectively. Many review and original studies reviewed in this study has some sort of biological measurements such as blood or urine tests. However, a dose-response relationship was not established, and clear mode of action for these heavy metals is not available even in animal studies. The seventh, eighth, ninth characteristic are coherence, experiment, and analogy, respectively. These three criterions are mainly applicable in experimental and clinical studies, and since this study reviews and compares others studies, such characteristics are not compatible with the approach used in this study.

Most of studies done to link a heavy metal to CVDs are usually specified to link one heavy metal to one or more of CVDs. However, it is almost not possible to study more than one heavy metal at the same time and link them to certain CVDs. This difficulty existed due to the interactive effect of addition or synergism when more than one heavy metal exposure occurs at the same time as shown in Figure 3. Further, neither dose – response relationship of heavy metals nor mode of action is well – known for the four heavy metals selected in our study. [2-5] This adds more complexity to figure out the exact effect of each heavy metal on any of the CVDs.

Most of studies done for different heavy metals were either clinical studies for patients already having a CVD, or ecological studies specified for a particular region contaminated by a heavy metals. For example, arsenic studies were mostly done in areas contaminated with arsenic, especially in areas drinking from ground water, such as in Bangladesh, Chile, China, and Taiwan. [10] Most of the associations linking mercury to CVD were based on Finnish studies investigating the effect of methyl mercury accumulated in fish, and consumed by the general population. [17,18] This is the main source for organic mercury exposure. Dental amalgams contain

elemental (vapor) mercury, which is another source of exposure, especially to dentists. [1,2,20] Other sources for mercury exposure are not well defined in the general population, unless accidental exposures to mercury happen.

Cadmium studies were commonly clinical studies for patients who complained from symptoms found in some of the common CVDs. Their examination showed higher than normal cadmium blood concentrations. Other studies were ecological studies, examples for those are studies done in Belgium, Japan and in the United States. [5] In contrast, lead studies have been done over many places around the world and despite the facts that lead contamination in air, soil, and water from petroleum sources was a substantial public health problem, [10] lead has significantly decreased in the last few years in several developed countries due to the introduction of unleaded petrol. [10] Therefore, the general population's blood lead levels have decreased. [10] Yet, persistence of lead in the environment and its use in other industries keeps the risk, such as in battery; in glass; in food-can soldering; in ceramic glazes; in drinking water pipe systems, and in folk remedies. [1] The persistence of lead in the environment made its existence in soil and water of great chance to be in the food chain, [10] that is also true for other heavy metals. This persistent existence of heavy metals in the environment makes the general population under the detrimental effects of chronic exposure throughout the years. [1] Such effects occur through the accumulation of one or more of heavy metals or the irreversible toxic effect of chronic exposure. The effect of combination and/or interaction of one or two of the heavy metals is not known yet since complete understanding of mode of action for one heavy metal is not clear rather than it would be for two or more entering together as a mixture or at different time points.

The main objective of Figure 3 is to illustrate how shared critical toxic pathways of two or more of heavy metals would increase the probability of CVDs assuming an additive or synergistic relationship. We selected Arsenic & Lead for Figure 3. The reason is that both of them are more harmful to CVDs and they both suggestively share same critical toxic pathways, which lead to a CVD at the end. [3,4] This means that if two or more of the heavy metals or ''even other chemicals'' share same critical toxic pathways, they might lead to a CVD in a faster or in a more detrimental way, regardless if exposure happen at the same time or at two different times.

A well-defined mechanism of action for heavy metals has not been provided yet. However, oxidative stress was identified as an important key event in the toxicity of heavy metal in humans. [1] Oxidative stress presented by reactive oxygen species (ROS) is responsible for lipid peroxidation, nitric oxide disturbance that affect endothelial homeostasis and growth, and make changes in gene or proteins structure or function. [3,4] These changes can lead to Atherosclerosis. [1] Oxidative stress is also involved in the disturbance in Ca+ homeostasis by release of Ca+ from the mitochondria which might lead to hypertension , also Lead can have the same effect on Ca+ but by working as a substitute for Ca+ if interacting with calmodulin and calcium-dependent potassium channels. [3] Disturbance of renal function caused by oxidative stress produced by lead exposure is suggestive to be related to hypertension. [1] Main known ROS are superoxide (O_2^-), hydrogen peroxide (H_2O_2), and Hydroxyl radical (OH^-). These particles are normal products of metabolic reactions in the body. Body defense mechanisms can eradicate these particles and remove their toxic effects. Nevertheless, if this capacity is

overwhelmed, these products start to act adversely in the body.

Arsenic affects defense mechanisms of detoxification, including depletion of Metallothionein and Glutathione. [4] Metallothionein is a cyteine-rich small protein which binds to heavy metals and disperse it and/or store it in the body; as a way of intoxication. [21] Heavy metals induce Metallothionein syntheses when heavy metals are up to a certain level. However, depletion starts to happen when exposure levels to heavy metals are very high that all Metallothionein are bound and no more metallothioneinis synthesized. This process of induction then depletion is also true for glutathione. [4] In addition, glutathione reduction occurs if arsenic binds to Glutatione peroxidase, Gluatathione S-transferase, or glutathione reductase, which is important enzyme in glutathione synthesis. [4] Reduction in Metallothionein and glutathione decreases tolerance and increases sensitivity towards heavy metals, which might lead to inflammatory genes induction, expression of proteins associated with inflammation, and increasing the probability for atherosclerosis. [1,4]

As noticed in this discussion, a likelihood of an adverse effect on the cardiovascular system might happen through a concurrent or a repetitive exposure from more than one heavy metal. However, it is not yet clear when and how an effect happen and through which mechanism. In addition to that, this article has a limitation in that such assumed associations, based on weight of evidence "weak, moderate, or strong", are subjective to the researchers view. Some reviewers and readers might assume a stronger or a weaker evidence for an association based on our criteria. However, consistency among studies is not possible, and the number of studies with high power and showing a clear association are not many.

CONCLUSION

This study summarized the weight of evidence of four heavy metals (Arsenic, Lead, Cadmium, and Mercury) associations' with five different cardiovascular diseases. The work of this study reveals the gap found in literature about the chronic effect of those heavy metals on CVDs, at the population level. Although data available for some heavy metals is more than the data available for other heavy metals, more research is needed for all of these heavy metals to confirm their effects in CVDs, and expand our understanding on their mechanisms of action. This will provide a great insight into assessing risk of these heavy metals and improve public health prevention plans for reducing CVDs incidence.

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